UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/640,081	08/13/2003	James M. Minor	10030208-1	7915

22878 7590 04/17/2007

AGILENT TECHNOLOGIES INC.
INTELLECTUAL PROPERTY ADMINISTRATION,LEGAL DEPT.
MS BLDG. E P.O. BOX 7599
LOVELAND, CO 80537

EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/640,081	MINOR, JAMES M.	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *24-29 and 35-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/07*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12/20/06*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Application No. 10640081, (20050037363 A1): Claims 1-41 are pending. Claims 24-29 and 35-41 are withdrawn. Claims 1-23 and 30-34 are examined.

Election/Restrictions

2. This application contains claims 24-29 and 35-41 drawn to an invention nonelected with traverse in the Paper entered 7/17/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application, 10/640,081, was filed 8/13/2003.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 1/16/07, was filed after the mailing date of the non-final rejection on 10/12/2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-23 and 30-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader. This rejection is necessitated by applicant's amendments to the claims.

The claims are drawn to a method of screening a combination of treatments to target a disease process comprising providing differential expression levels of diseased tissue samples.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

One of skill in the art cannot envision the detailed sequences of differential expression levels for the genus of disease processes. The specification does not provide any example, working or otherwise of differential gene sequence expression indicative of the genus of disease processes. The genus of disease processes includes many diseases known to or suspected of having a genetic association; however the identification of the genus of genes whose expression levels correlate with a disease and whose change would indicate treatment efficacy has not been accomplished for the wide genus of disease processes. The specification does not disclose a representative number of species of differential expression levels of diseased processes such that one of skill in the art would envision that applicant had possession of the full scope of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant

is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant has amended claim 1 to now state language "screening a combination of treatments to specifically target a disease process that impacts gene expression". Applicant argues that the instant invention is directed to screening a combination of treatments to specifically target a disease process. Applicant argues that the present invention correlates expression levels of genes whose expression levels are impacted by a disease process, with treatment response values after treating diseased tissues with various treatments.

Applicant further submits that the methods claimed in the present invention can be practiced with other genetic markers as they become available. Applicant states that "[I]n this regard, the claimed invention uses probes that are already known to be markers for a specific disease process and screens treatment of diseased tissues diseased by the disease process to identify combinations of treatment that are likely to be effective", (Reply at p. 12). Applicant points to the reference of Muraca, which is cited in the maintained rejection under 35 USC 103 (a), and states:

> Muraca, U.S. Patent Application Publication No. 2003/0049701, which was cited by the Examiner in the Office Action, discloses that the expression or form of a gene product can be used as a marker if it appears characteristically when a phenotype such as disease is observed. Muraca further discloses that numerous gene products have been shown to participate in or to be associated with human disease, and their measurement can provide diagnostic and prognostic tools to the clinician, see page 1, paragraph [0004]. Muraca notes that a range of levels of expression of a gene product might be associated with a phenotype A in which a cancer cell is relatively differentiated and respects its normal

> tissue boundaries, while an overlapping range of levels of expression may be associated with a phenotype B in which a cancer cell is relatively undifferentiated, but has not yet metastasized, and that it is difficult to make an accurate prognosis at the overlapping boundaries between phenotypes. Muraca further notes that this situation is complicated by the fact that a disease, such as cancer, represents the interactions of multiple genes, each of which may be expressed at varying levels.

Reply at pp. 12-13.

Applicant has provided a press release regarding Exonhit Therapeutics for the disclosure that well-defined disease genetic markers are known for neurodegenerative disease and cancers. Applicant has provided a news story by Ann M. Thayer that states that Avalon Pharmaceuticals "has taken about 2,000 genes and generated gene expression profiles of all known or potential anticancer agents to create a transcriptional structure-activity relationship database. The company says it can then optimize new drug candidates by comparing their gene expression profiles to the expression signatures of the reference compounds."

Applicant's arguments, entered 1/16/2007, have been fully considered but they are not persuasive. The specification does not describe an representative number of combination of genes whose expression correlate with a disease state, nor a single working embodiment of combinations of genes, that correlate after-treatment expression levels of genes whose expression levels are impacted by a disease process, such that one of skill in the art would envision that applicant had possession of the full breadth of the invention as claimed.

Applicant cites publications that generating gene expression profiles to thousands of genes in response to all known or potential anticancer agents are well

known in the art. However, the use of arrays comprising thousands of genes to examine expression profiles for diseases and treatments thereof, (and as encompassed by the instant claims when broadly, but reasonably read), are not predictable.

For example, and solely to address applicant's arguments, the examiner respectfully notes that the 2006 publication of Paik, Molecular Profiling of Breast Cancer, Curr Opin Obstet Gynecol 18: 59-63 (2006), states:

> Microarray-based gene-expression-profiling methods produce literally 10 000 to 60 000 data points for each clinical case, depending on which platform is used. Mining the vast amount of expression data, and trying to build a prognostic profile, is not a simple task [6]. First, the number of variables is much larger than the sample size in all studies published so far. Therefore, the false discovery rate is expected to be very high. So far, not one of the studies using microarrays has had a large enough sample size, at least from many statisticians' points of view [6].

Paik at p. 60, para 2. Paik further states:

> In conclusion, microarray-based markers, although very promising, are not yet ready for widespread use. The technology will have to evolve further to make a clear clinical impact. Also needed is the development of a robust method to interrogate degraded RNA that has been extracted from formalin-fixed paraffin-embedded tumor tissue, thus introducing increased reproducibility, but more importantly integration of conventional markers, into the single prognostic model. Although some efforts are being made in that regard, lack of sample size is a serious limitation and will not be easily resolved because of the requirement for frozen tumor tissue [19•].

Paik at p. 61, para 3. Therefore, it is respectfully submitted that the correlation of expression of multiple genes in combination on a microarray, and for any disease state, is not predictable, despite the publications that applicants provide.

Therefore, it is respectfully submitted that one of skill in the art would not envision that applicant had possession of the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is necessitated by applicant's amendments to the claims.

Claim 1 states the language "screening a combination of treatments to specifically target a disease process that impacts gene expression", which renders the claim vague and indefinite, because it is unclear whether it is the "combination of treatments" or the "disease process" that impacts gene expression.

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1-4, 6-22, 30-33, are rejected under 35 U.S.C. 103(a) as being unpatentable over Muraca, US Publication 20030049701 A1, in view of Glinskii, US Publication 20040053317 A1.

This rejection is maintained for the reasons of record as set forth in the previous Office action. That rejection is copied below for the convenience of the reader.

The claims are drawn to a method for screening a combination of treatments to specifically target a disease process comprising:

-providing differential expression levels of disease tissue samples as features of microarrays;
-treating the disease tissue samples
-generating a phenotypic signature representing the treatment response
-repeating the aforementioned steps
-performing a clustering operation based on the phenotypic/genotypic signatures;
-selecting treatments; and variations thereof.

Muraca, US Publication 20030049701 A1, throughout the publication, and at para [0006], [0014]-[0017], [0023], [0205], teach oncology microarrays upon which samples from patients treated with chemotherapy, etc. may be assayed. Muraca, at para [0035], teach guiding treatment based on the comparative levels of one or more cell-growth related polypeptides.

Muraca at para [0044], [0062]-[0065] disclose a computer–assessable file regarding a collection of information regarding a tissue sample, reading on remote transmission of data.

Muraca does not disclose performing a clustering operation based on phenotypic or genotypic signatures.

Glinskii, US Publication 20040053317 A1, throughout the publication, and e.g., at para [0407], teaches the use of Affymetrix arrays for assaying gene expression, and at, e.g., para [0413]-0421], [0426], teaches the use of clustering methods to analyze gene expression profiles. Glinskii, at para [0413], teaches that clinically relevant genetic signatures can be found by searching for clusters of co-regulated genes.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used method for screening a combination of treatments to specifically target a disease process comprising performing a clustering operation based on the phenotypic/genotypic signatures.

In regard to the use of density center analysis, such use would be an inherent feature of cluster analysis, as taught by Glinskii.

In regard to two-color or two channel microarray processes, such uses would be obvious over the Affymetrix array techniques taught by Glinskii.

In regard to the various efficacies and toxicities in screening combinations of treatments, such considerations would be obvious in view of the clinical setting taught by Muraca.

One of ordinary skill in the art would have been motivated to make and use methods comprising performing a clustering operation based on the phenotypic/genotypic signatures because Glinskii teaches that clinically relevant genetic signatures can be found by searching for clusters of co-regulated genes

One of ordinary skill in the art would have had a reasonable expectation of success in using clustering methods for selecting treatments, because Glinskii at, e.g., para [0426], teaches identifying human prostate tumor gene clusters using clustering analysis.

Response to Arguments

Applicant argues that Muraca does not compare phenotypic response signature of disease tissues with signatures of differential expression levels of the diseased tissues when untreated.

Applicant's arguments, entered 1/16/2007, have been fully considered but they are not persuasive.

Muraca states:

> [0023] The invention provides oncology microarrays which comprise a substrate on which a plurality of tissue and/or cell samples are provided, each sample being stably associated with the substrate at a different, known, position on the substrate. Preferably, samples represent different types or stages of cancer. Samples can be ordered on the substrate of a microarray into groups according to common characteristics of the patients from whom the samples are obtained (e.g., a group of samples from patients treated with chemotherapy, a group of samples from patients not treated with chemotherapy, a group from patients treated with hormones, a group from patients not treated with hormones, etc.). By dividing samples on the substrate into different groupings representing different cell/tissue types, subtypes, histological lesions, and clinical subgroups, the microarrays according to the invention enable ultra-high-throughput molecular profiling

Muraca at para [0023]. Thus Muraca compares the phenotypic response signature of disease tissues with signatures of differential expression levels of the diseased tissues when untreated.

Claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). See, *e.g.*, *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The claims are drawn to methods that, in part, comprise providing a differential expression level signature for each disease tissue sample, and treating the diseased tissue samples with a treating, and then generating a phenotypic signature representing the treatment-response values.

However, it is respectfully noted that the instant specification states:

> [0024] It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a sample" includes a plurality of such samples and reference to "the microarray" includes reference to one or more microarrays and equivalents thereof known to those skilled in the art, and so forth.

Specification at para [0024]. Therefore, the examiner respectfully submits that Muraca providing a differential expression level signature for each disease tissue sample, and treating the diseased tissue samples with a treating, and then generating a phenotypic signature representing the treatment-response values.

The examiner agrees that James Minor is the sole inventor, and thanks the applicant for correcting the record.

Conclusion

11. Claims 1-23 and 30-34 are rejected.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya, whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya, Ph.D.
Primary Examiner
Art Unit 1639